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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

(54) Piperidine Derivatives

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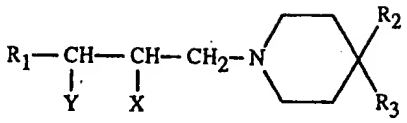
Piperidine derivatives

Abstract

Compounds of the formula I



(I)

in which X, Y, R_1, R_2 and R_3 are as defined in the description have valuable pharmaceutical properties and are effective, in particular, against tumours. They are prepared in a manner known per se.

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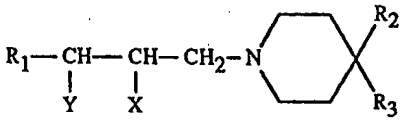
Piperidine derivatives

The invention relates to compounds of the formula I



(I)

in which R_1 is C_1-C_{30}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano or lower alkyl which is substituted by hydroxyl, lower alkoxy, acyloxy, amino, lower alkylamino, di-lower alkylamino or acylamino; R_3 is hydrogen, lower alkyl or aryl; one of the radicals X and Y is hydroxyl, lower alkoxy or acyloxy and the other of the radicals X and Y is hydrogen; or both radicals X and Y can also be hydrogen, if R_2 is cyano or lower alkyl substituted by amino or acylamino and R_1 is C_2-C_{30}alkyl; and to salts thereof, processes for the preparation of these compounds, pharmaceutical formulations containing these compounds and the use of these compounds for the therapeutic treatment of the human or animal body or for the preparation of pharmaceutical formulations.

Within the scope of the present application, the general terms used above and below have the following meanings:

The prefix "lower" means a radical having 1 to 7 and particularly 1 to 4 carbon atoms.

Lower alkyl - as such and also in composite terms, for example lower alkoxycarbonyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, lower alkoxy, lower alkylamino or di-lower alkylamino - is, for example, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, n-pentyl, neopentyl, n-hexyl or n-heptyl, preferably ethyl and particularly methyl.

C_1-C_{30}alkyl is preferably linear C_1-C_{30}alkyl, but can also be branched and is, for example,

lower alkyl as defined above or, for example, n-octyl, n-nonyl, n-decyl, n-undecyl, n-tridecyl or n-pentadecyl, or, for example, 2,7-dimethyloctyl. C_1-C_{30}alkyl is especially C_1-C_{19}alkyl, particularly C_1-C_{15}alkyl and primarily C_7-C_{15}alkyl.

C_2-C_{30}alkyl is the same as C_1-C_{30}alkyl with the exception of methyl and is especially C_2-C_{19}alkyl and primarily C_7-C_{15}alkyl.

An acyloxy radical X or Y is, for example, arylcarbonyloxy, aryl-lower alkanoyloxy, halogeno-lower alkanoyloxy, C_1-C_{30}alkanoyloxy, carbamoyloxy, N-lower alkylcarbamoyloxy, N-aryl-lower alkylcarbamoyloxy or N-arylcarbamoyloxy, especially C_1-C_{18}alkanoyloxy or N-phenyl-lower alkylcarbamoyloxy and primarily C_1-C_{12}alkanoyloxy.

In general, acyloxy is, for example, arycarbonyloxy, aryl-lower alkanoyloxy, halogeno-lower alkanoyloxy or lower alkanoyloxy, preferably lower alkanoyloxy.

Acylamino is, for example, arylcarbonylamino, aryl-lower alkanoylamino, halogeno-lower alkanoylamino or lower alkanoylamino, especially lower alkanoylamino.

Aryl - as such and also in composite terms, for example arylcarbonyloxy, aryl-lower alkanoyloxy, arylcarbonylamino or aryl-lower alkanoylamino - is, for example, phenyl or naphthyl, such as 1-naphthyl or 2-naphthyl, or substituted phenyl or naphthyl, for example phenyl or naphthyl each of which is substituted by lower alkyl, halogeno-lower alkyl, hydroxyl, lower alkoxy, lower alkanoyloxy, halogen and/or nitro. Aryl is preferably phenyl which is unsubstituted or substituted as indicated above, especially phenyl.

Arylcarbonyloxy (≙aroyloxy) is, for example, benzoyloxy or naphthoyloxy.

Aryl-lower alkanoyloxy is, for example, phenyl-lower alkanoyloxy, such as phenylacetoxy or phenylpropionyloxy.

Halogeno-lower alkanoyloxy is, for example, trifluoroacetoxy.

C_1-C_{30}alkanoyloxy is, for example, palmitoyloxy, stearoyloxy or lower alkanoyloxy.

Lower alkanoyloxy is, for example, acetoxy, propionyloxy or pivaloyloxy and also, for

example, formyloxy.

Arylcarbonylamino (≙ aroylamino) is, for example, benzoylamino or naphthoylamino.

Aryl-lower alkanoylamino is, for example, phenyl-lower alkanoylamino, such as phenylacetylamino or phenylpropionylamino.

Halogeno-lower alkanoylamino is, for example, trifluoroacetylamino.

Lower alkanoylamino is, for example, acetylamino, propionylamino or pivaloylamino and also, for example, formylamino.

Halogen is, for example, fluorine or iodine, especially bromine and particularly chlorine.

Halogeno-lower alkyl is, for example, trifluoromethyl.

Salts of compounds according to the invention are primarily pharmaceutically acceptable non-toxic salts. For example, compounds of the formula I having basic groups can form acid addition salts, for example with inorganic acids, such as hydrochloric acid, sulfuric acid or phosphoric acid, or with suitable organic carboxylic or sulfonic acids, for example acetic acid, fumaric acid or methanesulfonic acid, or, for example, with amino acids, such as arginine, or lysine. If several basic groups are present mono-salts or poly-salts can be formed. Compounds of the formula I having an acid group, for example carboxyl, and a basic group, for example amino, can exist, for example, in the form of internal salts, i.e. in a zwitter ion form, or one moiety of the molecule can exist as an internal salt and another moiety as a normal salt.

Salts which are unsuitable for use as pharmaceuticals, for example picrates or perchlorates, can also be used for isolation or purification. Only the pharmaceutically acceptable non-toxic salts are suitable for therapeutic application, and these are therefore preferred.

Depending on their structure, the compounds of the present invention can exist in the form of mixtures of isomers or pure isomers.

The compounds, according to the invention, of the formula I display valuable properties,

in particular properties which can be used in pharmacology. In particular, they exhibit a strong inhibiting action on protein kinase C. Protein kinase C, which is dependent on phospholipids and calcium, occurs within the cell in several forms and takes part in various fundamental processes, such as the transmission of signals, proliferation and differentiation and also the secretion of hormones and neurotransmitters. As is known, the activation of these enzymes takes place either through a hydrolysis of phospholipids of the cell membrane, brought about via receptors, or through a direct interaction with certain tumour-promoting active ingredients. The signal transmission via degradation of inositolphospholipids, brought about by receptors, can be influenced by the modulation of the activity of protein kinase C. Substances which are capable of modifying the activity of protein kinase C selectively, such as the compounds of the formula I, can be used as tumour-inhibiting, immuno-modulating, anti-inflammatory, anti-bacterial and anti-parasitic active ingredients, such as anti-trypanozidal or anti-malarial active ingredients.

In addition, the compounds according to the invention have an antiviral action and can be of interest, for example, for the treatment of diseases induced by HIV virus, such as ARC or AIDS.

The valuable pharmacological properties of the compounds according to the invention can be demonstrated, for example, by means of the following biological standard tests: 1. Modulation of the action of protein kinase C (from rats' brain); 2. Anti-proliferative action against, for example, human T24 carcinoma of the bladder in vitro; 3. Anti-tumour action in vivo, for example in human T24 bladder xenografts and MBA 9812 lung xenografts on hairless mice; and 4. Inhibition of HIV-reverse transcriptase and DNA-polymerase.

The effective concentrations of the compounds according to the invention which result in a 50% inhibition in the in vitro tests (IC 50 values) are minimal at approx. 10 nM, and the effective doses in in vivo experiments correspond at the most to one fifth of the maximum tolerated dose and are between approx. 0.5 and 50 mg/kg.

The compounds of the formula I are therefore suitable, for example, for the treatment of benign and malignant tumours. They can cause regression of tumours and also prevent the propagation of tumour cells and the growth of micrometastases.

The compounds of the formula I in which R_2 is cyano are also valuable intermediates for the preparation of other compounds of the formula I, for example those in which R_2 is aminomethyl. The latter can be prepared from the former by reduction, for instance using lithium aluminium hydride and aluminium trichloride.

Preferred compounds of the formula I are those in which R_1 is C_1-C_{19}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano or lower alkyl which is substituted by hydroxyl, lower alkoxy, lower alkanoyloxy, amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino; R_3 is hydrogen, lower alkyl or phenyl; one of the radicals X and Y is hydroxyl, lower alkoxy, C_1-C_{18}alkanoyloxy, carbamoyloxy, N-lower alkylcarbamoyloxy, N-phenyl-lower alkylcarbamoyloxy or N-phenylcarbamoyloxy and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is cyano or lower alkyl substituted by amino or lower alkanoylamino and R_1 is C_2-C_{19}alkyl; phenyl radicals being unsubstituted or substituted by lower alkyl, halogeno-lower alkyl, hydroxyl, lower alkoxy, lower alkanoyloxy, halogen and/or nitro; and salts thereof.

Compounds of the formula I which are particularly preferred are those in which R_1 is C_1-C_{15}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, cyano or lower alkyl which is substituted by hydroxyl, amino or lower alkanoylamino; R_3 is hydrogen, lower alkyl or phenyl; one of the radicals X and Y is hydroxyl, C_1-C_{12}alkanoyloxy or N-phenyl-lower alkylcarbamoyloxy and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is aminomethyl and R_1 is C_2-C_{15}alkyl; and salts thereof.

Compounds of the formula I which are primarily preferred are those in which R_1 is C_7-C_{15}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, hydroxymethyl, aminomethyl or lower alkanoylaminomethyl; R_3 is hydrogen, methyl or phenyl; one of the radicals X and Y is hydroxyl and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is aminomethyl; and salts thereof.

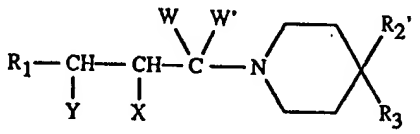
Compounds of the formula I which are particularly preferred are those in which R_1 is C_7-C_{15}alkyl, R_2 is aminomethyl, R_3 is phenyl and (a) X is hydroxyl and Y is hydrogen, or (b) X is hydrogen and Y is hydroxyl, or (c) X and Y are hydrogen; and salts thereof.

The invention relates particularly to the specific compounds described in the Examples

and to salts thereof which can be used as pharmaceuticals.

The compounds of the formula I can be prepared in a manner known per se, for example

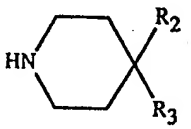
(a) by reducing a compound of the formula II



(II)

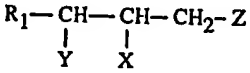
in which R_1, R_3, X and Y are as defined under formula I, R_2' is a group which can be converted by reduction into a radical R_2, or, if W and W' together are oxo, R_2' is also a radical R_2 as defined under formula I, and W and W' together are an oxo group or are two hydrogen atoms, or

(b) by alkylating a compound of the formula III



(III)

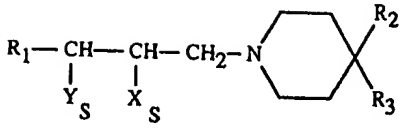
in which R_2 and R_3 are as defined under formula I, by means of a compound of the formula IV



(IV)

in which R_1, X and Y are as defined under formula I and Z is a nucleofugic detachable group and X and Z together can also be an epoxy group, or

(c) in order to prepare compounds of the formula I in which X or Y is hydroxyl, by removing the hydroxyl protective group in a compound of the formula V



(V)

in which R_1, R_2 and R_3 are as defined under formula I, one of the radicals X_s and Y_s is a hydroxyl group protected by a protective group and the other of the radicals X_s and Y_s is hydrogen; and/or, if desired, by converting a resulting compound of the formula I into another compound of the formula I, and/or, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting free compound of the formula I into a salt, and/or resolving a resulting mixture of isomeric compounds of the formula I into the individual isomers.

In the following detailed description of the processes a)-c), the symbols R_1, R_2, R_3, X and Y are each as defined under formula I, unless stated otherwise.

Process (a): Examples of groups R_2' which can be converted by reduction into a radical R_2 are cyano and carbamoyl, which are converted in a normal manner into aminomethyl under the reductive conditions selected, or lower alkoxycarbonyl and carboxyl, which are converted into hydroxymethyl under the reductive conditions selected.

If R_2' in the compound of the formula II is cyano, the reduction according to process (a) is carried out, for example, using a mixture of lithium aluminium hydride ($LiAlH_4$) and aluminium trichloride.

Compounds of the formula II in which R_2' is carbamoyl, lower alkoxycarbonyl or carboxyl are reduced, for example, by means of $LiAlH_4$ on its own.

The starting compounds of the formula II in which W and W' together are oxo (=O) are prepared, for example, by acylating a compound analogous to the formula III which contains, instead of the radical R_2, a group R_2' as defined under formula II, by means of an acid of the formula R_1-CHY-CHX-COOH or a reactive derivative thereof, for instance an acid halide or anhydride. The starting compounds of the formula II in which W and W' are two hydrogen atoms correspond, as a rule, to compounds of the formula I and are prepared, for example, by process (b) or (c).

Process (b): The reaction according to process (b) proceeds in line with a conventional nucleophilic substitution reaction. In the course of this the secondary nitrogen atom in a compound of the formula III is alkylated.

If appropriate, the reaction is carried out in the presence of inorganic or organic acid-binding agents, for example tertiary amines, for instance triethylamine, or potassium carbonate.

Examples of a nucleofugic detachable group Z in a compound of the formula IV are halogen, in particular chlorine, bromine or iodine, or sulfonyloxy substituted by aliphatic or aromatic groups, for example methylsulfonyloxy or 4-methylphenylsulfonyloxy.

If X and Z in a compound of the formula IV together are an epoxy group (ˋOˊ), compounds of the formula I in which X is hydroxyl are obtained when process (b) is carried out.

The starting compounds of the formulae III and IV are known per se or can be prepared analogously to known compounds.

Process (c): A hydroxyl group X_s or Y_s protected by a protective group is, for example, organic silyloxy, in particular tri-lower alkylsilyloxy, for example trimethylsilyloxy, dimethyl-tert-butylsilyl and especially dimethyl-thexylsilyloxy (thexyl ≙ 2,3-dimethyl-2-butyl), or acyloxy, in particular lower alkanoyloxy, for example formyloxy, acetoxy or pivaloyloxy; halogeno-lower alkanoyloxy, for example chloroacetoxy, dichloroacetoxy, trichloroacetoxy or trifluoroacetoxy; lower alkoxy-lower alkanoyloxy, for example methoxyacetoxy; aryl-lower alkoxy-lower alkanoyloxy, for example triphenylmethoxyacetoxy; aryloxy-lower alkanoyloxy, for example phenoxyacetoxy; benzoyloxy; lower alkoxycarbonyloxy, for example methoxycarbonyloxy, ethoxycarbonyloxy or tert-butoxycarbonyloxy; or aryl-lower alkoxycarbonyloxy, for example benzyloxycarbonyloxy or diphenylmethoxycarbonyloxy each of which is unsubstituted or substituted by nitro.

The removal of the hydroxyl protective group in process (c) is effected in a manner known per se by solvolysis, in particular hydrolysis, or alcoholysis. Organic silyl is removed, for example, by treatment with water, hydrochloric acid or methanol. Examples of preferred systems for the removal of organic silyl are (a) acetic acid/tetrahydrofuran/water, (b) 1% concentrated hydrochloric acid in ethanol, (c) the hydrogen fluoride/urea complex in

concentrated hydrochloric acid in ethanol, (c) the hydrogen fluoride/urea complex in cyclohexane, (d) tetrabutylammonium fluoride in tetrahydrofuran and (e) trifluoroacetic acid/acetonitrile/water. Acyl groups are removed especially by alcoholysis, but also hydrolysis, in the presence of a base, for example sodium ethoxide or hydroxide or potassium ethoxide or hydroxide.

The starting compounds of the formula V are prepared, for example, by carrying out one of the processes (a) and (b) for the preparation of compounds of the formula I or carrying out a conversion of a compound of the formula I into another compound of the formula I having a protected hydroxyl group X or Y.

Compounds of the formula I can be converted into other compounds of the formula I.

For example, compounds of the formula I in which R_2 is cyano can be converted into compounds of the formula I in which R_2 is aminomethyl by reduction, as described in process (a), for instance using a mixture of $LiAlH_4$ and $AlCl_3$.

Compounds of the formula I in which R_2 is carbamoyl or lower alkoxycarbonyl or carboxyl can also be converted into compounds of the formula I in which R_2 is aminomethyl or hydroxymethyl, respectively, by reduction, as described in process (a), for example using $LiAlH_4$.

Compounds of the formula I in which R_2 is lower alkoxycarbonyl can be converted into compounds of the formula I in which R_2 is carboxyl by hydrolysis, for example in a basic medium, for instance using NaOH or KOH in lower alkanols.

Compounds of the formula I in which X or Y is hydroxyl can be converted into compounds of the formula I in which X or Y is lower alkoxy or acyloxy by reaction with lower alkylating agents or acylating agents, respectively. Examples of suitable lower alkylating agents are lower alkyl halides, mesylates or tosylates, which are preferably used in the presence of strong bases, for example sodium hydride. Examples of suitable acylating agents are alkanecarboxylic acids, in particular reactive derivatives thereof, such as acid chlorides or anhydrides, which are preferably used in the presence of inorganic or organic acid-binding agents. If the acylation of the OH group X or Y is carried out using, for example, lower alkyl, phenyl-lower alkyl or phenyl isocyanates, compounds of the formula I in which X or Y is N-lower alkylcarbamoyloxy, N-phenyl-lower

alkylcarbamoyloxy or N-phenylcarbamoyloxy are obtained.

Conversely, the compounds of the formula I in which X or Y is carbamoyloxy, N-lower alkylcarbamoyloxy, N-phenyl-lower alkylcarbamoyloxy or N-phenylcarbamoyloxy can be re-converted into the analogous compounds of the formula I in which X or Y, respectively, is hydroxyl, for example by hydrolysis using sodium hydroxide solution or by reduction with $LiAlH_4$.

If the OH group X or Y in a compound of the formula I is acylated with an optically active isocyanate, for example (-)-1-phenylethyl isocyanate, a mixture of diastereomers of urethanes is obtained. The individual diastereomers can be separated and can be converted into the pure enantiomers of the compounds of the formula I in which X or Y, respectively, is hydroxyl, for example by hydrolysis with sodium hydroxide solution or by reduction with $LiAlH_4$.

Free compounds of the formula I obtainable in accordance with the process and having salt-forming properties can be converted into their salts in a manner known per se, compounds having basic properties by treatment with acids or suitable derivatives thereof, and compounds having acid properties by treatment with bases or suitable derivatives thereof.

Mixtures of isomers obtainable in accordance with the invention can be resolved into the individual isomers in a manner known per se, racemates, for example, by forming salts with optically pure, salt-forming reagents and separating the mixture of diastereomers thus obtainable, for example by means of fractional crystallization.

If optically active starting compounds are employed in the processes (a), (b) and (c) for the preparation of compounds of the formula I, in particular optically active epoxides of the formula IV in process (b), the individual isomers are obtained without further treatment when the corresponding processes are carried out.

The reactions mentioned above can be carried out under reaction conditions known per se, in the absence, or usually in the presence, of solvents or diluents, preferably those which are inert towards the reagents used and dissolve the latter, in the absence or presence of catalysts, condensation agents or neutralizing agents, depending on the type of reaction and/or the reactants at a reduced, normal or elevated temperature, for example within the

temperature range from about -70°C to about 190°C, preferably from about -20°C to about 150°C, for example at the boiling point of the solvent used, under atmospheric pressure or in a closed vessel, if appropriate under pressure, and/or in an inert atmosphere, for example under an atmosphere of nitrogen.

It is preferable to employ, in the process of the present invention, starting materials which result in the compounds described initially as particularly valuable.

The invention also relates to embodiments of the process in which a compound obtainable as an intermediate at any desired stage of the process is used as the starting material and the missing process stages are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example a salt thereof.

The present invention also relates to pharmaceutical formulations, containing one of the pharmacologically active compounds of the formula I as the active ingredient. Formulations for enteral, in particular oral, administration, and also for parenteral administration are particularly preferred. The formulations contain the active ingredient on its own or, preferably, together with a pharmaceutically acceptable carrier. The dosage of the active ingredient depends on the disease to be treated, and also on the species, age, weight and individual condition and also on the mode of administration.

The pharmaceutical formulations contain from about 5% to about 95% of the active ingredient, administration forms for individual dosage preferably containing from about 20% to about 90% and administration forms not for individual dosage preferably containing about 5% to about 20% of active ingredient. Dosage unit forms, such as coated tablets, tablets or capsules, contain from about 0.01 g to about 1.0 g of the active ingredient.

The pharmaceutical formulations of the present invention are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. Thus pharmaceutical compositions for oral use can be obtained by combining the active ingredient with one or more solid carriers, if appropriate granulating a resulting mixture, and, if desired, processing the mixture or granules to give tablets or sugar-coated tablet cores, if appropriate by adding additional adjuncts.

Suitable carriers are especially fillers, such as sugars, for example lactose, sucrose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tricalcium phosphate or calcium hydrogen phosphate, and also binders, such as starches, for example maize, wheat, rice or potato starch, methyl cellulose, hydroxypropyl methyl cellulose, sodium carboxymethyl cellulose and/or polyvinyl pyrrolidone, and/or, if desired, disintegrators, such as the abovementioned starches, and also carboxymethyl-starch, crosslinked polyvinyl pyrrolidone or alginic acid or a salt thereof, such as sodium alginate. Additional adjuncts are primarily glidants and lubricants, for example silica, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol or derivatives thereof.

Sugar-coated tablet cores can be provided with suitable coatings, if desired coatings resistant to gastric juices, using, inter alia, concentrated sugar solutions, which can contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, lacquer solutions in suitable organic solvents or solvent mixtures, or, for the preparation of coatings resistant to gastric juices, solutions of suitable cellulose preparations, such as acetyl cellulose phthalate or hydroxypropyl methyl cellulose phthalate. Dyes or pigments can be added to the tablets or sugar coatings, for example for identifying or characterizing different doses of active ingredient.

Other pharmaceutical compositions which can be administered orally are dry-filled capsules made of gelatin and also soft, closed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The dry-filled capsules can contain the active ingredient in the form of granules, for example mixed with fillers, such as maize starch, binders and/or lubricants, such as talc or magnesium stearate, and, if appropriate, stabilizers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquid adjuncts, such as fatty oils, paraffin oil or liquid polyethylene glycols, it being also possible to add stabilizers.

Examples of other oral administration forms are syrups prepared in a customary manner which contain the active ingredient, for example in a suspended form and in a concentration of approx. 5% to 20%, preferably approx. 10% or in a similar concentration which, for example when 5 or 10 ml are measured out, gives a suitable individual dose. Further, for example, pulverulent or liquid concentrates are also suitable for the preparation of shakes, for example in milk. Concentrates of this type can also be packaged in individual dose quantities.

Suppositories which consist of a combination of the active ingredient with a suppository base composition are, for example, suitable for use as pharmaceutical formulations which can be administered rectally. Examples of suitable suppository base compositions are natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols.

Aqueous solutions of an active ingredient in water-soluble form, for example a water-soluble salt, or aqueous injection suspensions containing substances which increase the viscosity, for example sodium carboxymethyl cellulose, sorbitol and/or dextran and, if appropriate, stabilizers are primarily suitable for parenteral administration. In this respect the active ingredient, without or together with adjuncts, can also be in the form of a lyophilizate and can be brought into solution by adding suitable solvents before parenteral administration.

Solutions, such as are used, for example, for parenteral administration, can also be used as infusion solutions.

The invention also relates to a method of treating the abovementioned states of disease. The compounds of the present invention can be administered prophylactically or therapeutically, being preferably used in the form of pharmaceutical formulations. In this respect a daily dose of about 0.05 g to about 5 g, preferably of about 0.1 g to about 1 g, of a compound of the present invention is administered for a body weight of about 70 kg.

The following examples illustrate the present invention; temperatures are quoted in degrees Centigrade. The following abbreviations are used: THF $\hat{=}$ tetrahydrofuran; ether $\hat{=}$ diethyl ether; abs. $\hat{=}$ absolute; conc. $\hat{=}$ concentrated.

Example 1: (a) 4-Cyano-1-(2'-hydroxy-1'-decyl)-4-phenylpiperidine

18.72 g (0.12 mol) of 1,2-epoxydecane (Aldrich) are dissolved in 180 ml of ethanol, 26.72 g (0.12 mol) of 4-cyano-4-phenylpiperidine hydrochloride (Aldrich) and 16.56 g (0.12 mol) of potassium carbonate are added and the mixture is heated under reflux for 6 hours. After cooling, the inorganic salts are filtered off, the filtrate is evaporated and the residue is dissolved in 100 ml of methylene chloride and washed with saturated sodium bicarbonate and saturated sodium chloride solution. The organic phase is then dried over magnesium sulfate and evaporated. The resulting oil is triturated with petroleum ether and

melting point 77-79°.

The following compounds are prepared analogously to Example 1a:

(b) 4-Cyano-1-(2'-hydroxy-1'-hexyl)-4-phenylpiperidine, melting point 55-58°.

(c) 4-Cyano-1-(2'-hydroxy-1'-octyl)-4-phenylpiperidine, melting point 61-63°.

(d) 4-Cyano-1-(2'-hydroxy-1'-dodecyl)-4-phenylpiperidine, melting point 54-56°.

(e) 4-Cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine.

50.4 g (0.24 mol) of 1,2-epoxytetradecane (Aldrich) are dissolved in 300 ml of ethanol, 54.4 g (0.24 mol) of 4-cyano-4-phenylpiperidine hydrochloride (Aldrich) and 33.2 g (0.24 mol) of potassium carbonate are added and the mixture is heated under reflux for 5 hours. After cooling, the inorganic salts are filtered off, the filtrate is evaporated and the residue is dissolved in 300 ml of ether and washed with 100 ml of water and 50 ml of saturated sodium chloride solution. The organic phase is then dried over potassium carbonate and is concentrated to half its volume. 100 ml of petroleum ether are added and the mixture is allowed to stand at 0°. In the course of this the title compound crystallizes out and is filtered off, washed with cold petroleum ether and dried in a high vacuum. Melting point 68-69°.

(f) R-(-)-4-Cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine, melting point 69-70°.

(g) S-(+)-4-Cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine, IR (KBr): 2940, 2870, 2247 weak, 1550, 1468 cm^{-1}.

(h) 4-Cyano-1-(2'-hydroxy-1'-hexadecyl)-4-phenylpiperidine, melting point 67-69°.

(i) 4-Cyano-1-(2'-hydroxy-1'-octadecyl)-4-phenylpiperidine, melting point 88-90°.

(j) 4-Cyano-1-(2'-hydroxy-1'-butyl)-4-phenylpiperidine, melting point 73°.

Example 2: (a) 4-Aminomethyl-1-(2'-hydroxy-1'-decyl)-4-phenylpiperidine dihydrochloride

A solution of 23.8 g (0.179 mol) of aluminium trichloride in 360 ml of abs. THF is added dropwise, under nitrogen and at room temperature, to a suspension of 6.83 g (0.179 mol) of lithium aluminium hydride in 450 ml of abs. THF. The mixture is stirred for 15 minutes and is then warmed to 35°. A solution of 26.1 g (0.179 mol) of 4-cyano-1-(2'-hydroxy-1'-decyl)-4-phenylpiperidine (see Example 1a) in 450 ml of abs. THF is added dropwise to this mixture. The reaction mixture is then stirred for 2.5 hours at 40 to 50°. After it has cooled to room temperature, approx. 250 ml of concentrated sodium hydroxide solution are added cautiously until the mixture has an alkaline reaction. The emulsion is filtered through kieselguhr (Hyflo Super Cel, Fluka), the filtrate is extraced with ether and the

organic phase is dried over sodium sulfate and evaporated. The resulting residue is dissolved in a little ethanol and 51 ml of a 10% ethanolic solution of hydrogen chloride are added. In the course of this the title compound crystallizes out in needles; melting point 259-261°.

The following compounds are prepared analogously to Example 2a:

(b) 4-Aminomethyl-1-(2'-hydroxy-1'-hexyl)-4-phenylpiperidine dihydrochloride, melting point 254-256°.

(c) 4-Aminomethyl-1-(2'-hydroxy-1'-octyl)-4-phenylpiperidine dihydrochloride, melting point 243-245°.

(d) 4-Aminomethyl-1-(2'-hydroxy-1'-dodecyl)-4-phenylpiperidine dihydrochloride, melting point 250-253°.

(e) 4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine dihydrochloride. A solution of 10.6 g (0.08 mol) of aluminium trichloride in 160 ml of absolute tetrahydrofuran is added dropwise, under nitrogen and at room temperature, to a suspension of 3.0 g (0.08 mol) of lithium aluminium hydride in 200 ml of absolute tetrahydrofuran. The mixture is stirred for 15 minutes, and a solution of 13.4 g (0.034 mol) of 4-cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine (Example 1e) in 160 ml of abs. tetrahydrofuran is then added dropwise at 35°. The reaction mixture is then stirred for 3 hours at approx. 50°. After the mixture has cooled (0°), 120 ml of conc. sodium hydroxide solution are added cautiously until the mixture has an alkaline reaction. The emulsion is filtered through kieselguhr (Hyflo Super Cel, Fluka), the filtrate is extracted with ether and the organic phase is dried over sodium sulfate and evaporated. The residue is dissolved in a little ethanol, and a small excess of ethanolic hydrogen chloride is added. In the course of this the title compound crystallizes out. It is filtered off and dried. Melting point 238-243°; free base, melting point 71-72°.

(f) R-(-)-4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine dihydrochloride, melting point 240-243° (with brown coloration); free base, melting point 65-66°.

(g) 4-Aminomethyl-1-(2'-hydroxy-1'-hexadecyl)-4-phenylpiperidine dihydrochloride, melting point 243-245°; free base, melting point 76-77°.

(h) 4-Aminomethyl-1-(2'-hydroxy-1'-octadecyl)-4-phenylpiperidine dihydrochloride, melting point 252-254°.

(i) 4-Aminomethyl-1-(2'-hydroxy-1'-butyl)-4-phenylpiperidine dihydrochloride,

melting point 265-267°.

Example 3: (Two diastereomers of) 4-Cyano-1-[2'-(1"-phenylethylaminocarbonyloxy)-1'-tetradecyl]-4-phenylpiperidine

2.0 g (0.005 mol) of 4-cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine (Example 1e) are dissolved in 5 ml of methylene chloride, and 1.0 ml (0.0071 mol) of (-)-1-phenylethyl isocyanate (Fluka) is added at room temperature. When the reaction is complete (approx. 16 hours) the reaction solution is evaporated. A (-)-rotatory 4-cyano-1-[2'-(1"-phenylethylaminocarbonyloxy)-1'-tetradecyl] -4-phenylpiperidine (isomer A) can be obtained in a pure state, melting point 59-63°, $[\alpha]_D^{20} = -46.3° \pm 0.9°$ (c = 1 in ethanol), by recrystallization from methanol twice. The second 4-cyano-1-[2'-(1"-phenylethylaminocarbonyloxy)-1'-tetradecyl]-4-phenylpiperidine (isomer B), which is also (-)-rotatory, can also be obtained, in the form of an oil, $[\alpha]_D^{20} = -21.1°$ (c = 1 in ethanol), by chromatographing the mother liquors over silica gel 60 (mobile phase: 4:1 petroleum ether/ ethyl acetate). Under the chromatographic conditions indicated diastereomer A elutes first.

Example 4: (a) S-(+)-4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine dihydrochloride

A solution of 19.1 g (0.143 mol) of aluminium trichloride in 300 ml of abs. THF is added dropwise, at room temperature and under nitrogen, to a suspension of 5.67 g (0.143 mol) of lithium aluminium hydride in 390 ml of abs. THF. After 15 minutes a solution of 20.3 g (0.0372 mol) of 4-cyano-1-[2'-(1"-phenylethylaminocarbonyloxy)-1'-tetradecyl]-4-phenylpiperidine (isomer B, see Example 3) in 390 ml of abs. THF is added dropwise. The reaction mixture is stirred for 3.5 hours at 40 to 50°, cooled and hydrolysed by the addition of 400 ml of a 30% sodium hydroxide solution (cooling in an ice bath). The mixture is then diluted with 800 ml of ether and 200 ml of water and thoroughly shaken in a separating funnel. The aqueous phase is extracted with ether, and the organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue is dissolved in 20 ml of ethanol, and 50 ml of a saturated ethanolic solution of hydrogen chloride are added. The product crystallizes out on cooling. It is filtered off, washed with cold ethanol and dried in a high vacuum; melting point 234-238° (with brown coloration), $[\alpha]_D^{20} = +13.0° \pm 0.9°$ (c = 1 in methanol).

(b) R-(-)-4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpipe ridine

dihydrochloride is prepared analogously from isomer A (see Example 3), melting point 236-239° (with brown coloration), $[\alpha]_D^{20} = -13.6° \pm 0.9°$ (c = 1.1 in methanol).

Example 5: 4-Cyano-4-phenyl-1-tetradecylpiperidine

11 g (0.05 mol) of 4-cyano-4-phenylpiperidine hydrochloride (Aldrich), 41 g (0.3 mol) of potassium carbonate (ground, anhydrous) and 13 ml (0.05 mol) of tetradecyl bromide in 150 ml of acetonitrile are heated under reflux for 5 hours. After the mixture has cooled, the insoluble inorganic salts are filtered off, the filtrate is evaporated and the residue is taken up in methylene chloride and washed with water and saturated sodium chloride solution. The organic phase is dried over magnesium sulfate and evaporated and the residue is recrystallized from methanol; melting point 46-48°.

Example 6: 4-Aminomethyl-4-phenyl-1-tetradecylpiperidine

A solution of 11.9 g (0.089 mol) of aluminium trichloride in 175 ml of abs. THF is added dropwise, under nitrogen and at room temperature, to a suspension of 3.4 g (0.089 mol) of lithium aluminium hydride in 220 ml of abs. THF. The mixture is stirred for 15 minutes and is then warmed to 35°. A solution of 14.5 g (0.089 mol) of 4-cyano-4-phenyl-1-tetradecylpiperidine (see Example 5) in 175 ml of abs. THF is added dropwise to this mixture. The reaction mixture is then stirred for 3 hours at 40-50°. After it has cooled to room temperature, approx. 130 ml of conc. sodium hydroxide solution are added cautiously until the mixture has an alkaline reaction. The emulsion is filtered through kieselguhr (Hyflo Super Cel, Fluka), the filtrate is extracted with ether and the organic phase is dried over sodium sulfate and evaporated. The resulting residue is recrystallized from 95% methanol; melting point 44-46°.

Example 7: 1-Tetradecyl-4-piperidinecarboxamide

2.5 g (0.02 mol) of 4-piperidinecarboxamide (Jansen) are dissolved in 60 ml of acetonitrile, 8.2 g (0.06 mol) of potassium carbonate (ground, anhydrous) and 5.4 ml (0.02 mol) of tetradecyl bromide are added and the mixture is boiled under reflux for 22 hours, cooled and filtered. The solid is extracted with a 9:1 mixture of methylene chloride/ethanol; the filtrate and the extracts are then evaporated and the product is recrystallized from ethanol; melting point 120-125°.

Example 8: 4-Aminomethyl-1-tetradecylpiperidine dihydrochloride

A hot, saturated solution of 3.2 g (0.01 mol) of 1-tetradecyl-4-piperidinecarboxamide (see

Example 7) in 350 ml of abs. THF is added dropwise, under nitrogen and at room temperature, to a suspension of 1.7 g (0.045 mol) of lithium aluminium hydride in 50 ml of abs. THF. The reaction mixture is then heated under reflux for 7 hours and cooled, and 1.1 ml of water, 1.1 ml of 15% sodium hydroxide solution and 3.3 ml of water are added cautiously. After being filtered off, the inorganic salts are thoroughly washed with ether, and the ether phase is dried over sodium sulfate and evaporated. The resulting oil is dissolved in a little ethanol, and 2 equivalents of a 10% ethanolic solution of hydrogen chloride are added. In the course of this the product is precipitated. It is filtered off and dried; melting point 240° (decomposition).

Example 9: 1-(2'-Hydroxy-1'-tetradecyl)-4-piperidinecarboxamide
2.56 g (0.02 mol) of 1,2-epoxytetradecane (Aldrich), 4.24 g (0.02 mol) of 4-piperidinecarboxamide (Jansen) and 25 ml of ethanol are heated under reflux for 2 hours. The mixture is then cooled, 10 ml of ether are added and the product is filtered off; melting point 135-137°.

Example 10 4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-piperidine dihydrochloride
A solution of 3.4 g (0.01 mol) of 1-(2'-hydroxy-1'-tetradecyl)-4-piperidinecarboxamide (Example 9) in 80 ml of abs. THF is added dropwise, under nitrogen and at room temperature, to a suspension of 1.1 g (0.029 mol) of lithium aluminium hydride in 50 ml of abs. THF. The reaction mixture is then heated under reflux for 4 hours and cooled, and 1.1 ml of water, 1.1 ml of 15% sodium hydroxide solution and 3.3 ml of water are added cautiously and the mixture is filtered. The inorganic salts are washed thoroughly with ether and the combined organic phases are dried over sodium sulfate and evaporated. The resulting oil is dissolved in a little ethanol, and 2 equivalents of a 10% ethanolic solution of hydrogen chloride are added. In the course of this the product is precipitated. It is filtered off and dried; melting point 280°.

Example 11: Ethyl 1-(2'-hydroxy-1'-tetradecyl)-piperidine-4-carbo xylate
4.2 g (0.02 mol) of 1,2-epoxytetradecane and 3.1 g (0.02 mol) of ethyl piperidine-4-carboxylate in 20 ml of ethanol are heated under reflux for 5.5 hours. The reaction solution is then cooled and evaporated and the residue is recrystallized from aqueous ethanol; melting point 33-34°.

Example 12: 1-(2'-Hydroxy-1'-tetradecyl)-piperidine-4-carboxylic acid
18.5 g (0.05 mol) of ethyl 1-(2'-hydroxy-1'-tetradecyl)-piperidine-4-carboxylate (Example

11) are dissolved in 100 ml of ethanol, 50 ml of 2 N sodium hydroxide solution are added and the mixture is heated under reflux for 2 hours. The reaction solution is then neutralized at 0° with 2N hydrochloric acid (50 ml = 0.1 mol) and concentrated as far as possible. The residue is stirred with 400 ml of methylene chloride, dried over sodium sulfate and evaporated. The crystalline residue is triturated with 1:1 ether/petroleum ether, the mixture is filtered and the product is dried; melting point 140-145°.

Example 13: 4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-methylpiperidine dihydrochloride

0.99 g (0.002 mol) of 4-aminomethyl-1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine hydrochloride are dissolved in a 3% solution of conc. hydrochloric acid in ethanol and heated under reflux for 7 hours. After cooling, the reaction solution is evaporated, the residue is taken up in 50 ml of methylene chloride and the solution is washed with saturated sodium carbonate solution, dried over sodium sulfate and evaporated again. The oil thus obtained is dissolved in a little ethanol, 1.5 ml of a 10% ethanolic solution of hydrogen chloride are added and the mixture is concentrated somewhat and induced to crystallize by adding a little ether. The title compound decomposes at approx. 260°.

The starting compound is prepared as follows:

(a) Ethyl 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-piperidine-4-carboxylate: 1.84 g (0.005 mol) of ethyl 1-(2'-hydroxy-1'-tetradecyl)-piperidine-4-carboxylate (Example 11) and 0.34 g (0.005 mol) of imidazole are dissolved in 10 ml of dimethylformamide, and 0.89 ml (0.005 mol) of thexyldimethylchlorosilane (Fluka) [thexyl = 2,3-dimethyl-2-butyl] is added at room temperature and the mixture is stirred for 24 hours at room temperature. The mixture is evaporated, the residue is extracted with a 1:1 mixture of ether/petroleum ether, and the extract is washed with saturated sodium bicarbonate solution ($NaHCO_3$), dried over sodium sulfate and evaporated. The residue is chromatographed (silica gel 60, 2:1 ethyl acetate/petroleum ether). The title compound is eluted with the first fractions (Rf value = 0.88); IR: 1709 cm^{-1} (C=O), analysis: found:
C 69.9% H 12.2% N 2.5%, calculated: C 70.4% H 11.9% N 2.7%.

(b) Ethyl 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate: a solution of 18.2 g (0.035 mol) of ethyl 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-piperidine-4-carb oxylate in 50 ml of abs. THF is added dropwise, at -78° and under

nitrogen, to a solution of lithium diisopropylamide in 60 ml of abs. THF [prepared from 7.3 ml (0.052 mol) of diisopropylamine and 32.4 ml (0.052 mol) of a 1.6-molar solution of butyllithium in hexane]. After 1 hour at -78°, 2.2 ml (0.035 mol) of methyl iodide are added dropwise. The mixture is stirred at -78° for 2 hours, allowed to warm up to room temperature slowly and stirred overnight. The reaction mixture is hydrolysed by adding 5.5 ml of 50% acetic acid dropwise at 0°. The mixture is then diluted with ether, washed with saturated sodium bicarbonate solution and dried over sodium sulfate, and the solvent is distilled off in a rotary evaporator. Chromatography over silica gel 60 (1:9 ethyl acetate/petroleum ether) affords the title compound as an oil (Rf value = 0.44 in the above system).

(c) 1-(2'-Thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylic acid: 15.6 g (0.03 mol) of ethyl 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate are dissolved in 180 ml of ethanol, and 30 ml of 2N sodium hydroxide solution are added. The mixture is heated under reflux for 5 hours, cooled and neutralized with 30 ml of 2 N hydrochloric acid. The alcohol is distilled off, the residue is partitioned between methylene chloride and water, and the organic phase is dried over sodium sulfate, evaporated and dried in a high vacuum. The title compound thus obtained is used without further purification in the next stage of the synthesis.

(d) 4-Methyl-1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-piperidine-4-carboxamide: 21 g (0.042 mol) of 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylic acid are dissolved in 590 ml of abs. THF and cooled to 0°, and 43.7 ml of pyridine are added, followed by 43.7 ml (0.355 mol) of ethyl chloroformate, added dropwise. 135 ml of conc. ammonia solution are then immediately added dropwise and the mixture is diluted with 680 ml of water. It is extracted with ethyl acetate, and the organic phase is washed with saturated sodium bicarbonate solution ($NaHCO_3$), dried over sodium sulfate and evaporated. Purification is carried out by chromatography over silica gel 60 (4:1 methylene chloride/ethanol) (Rf value in this system = 0.52). The title compound is obtained as an oil and is employed in the next stage without further purification.

(e) 9.69 g (0.0195 mol) of 4-methyl-1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-piperidine-4-carboxamide are dissolved in 115 ml of abs. THF and are added dropwise, at room temperature and under nitrogen, to a suspension of 1.5 g (0.0388 mol) of lithium aluminium hydride in 115 ml of abs. THF. The mixture is then heated under reflux for 2 hours and is then cooled to 0° and hydrolysed by adding 1.5 ml of water, 1.5 ml of a 15%

sodium hydroxide solution and 4.5 ml of water. The mixture is diluted with 200 ml of ether and filtered, and the filtrate is washed with water, dried over sodium sulfate and evaporated. The product is purified by chromatography over silica gel 60 (150:50:1 chloroform/methanol/concentrated ammonia solution) and is converted into the dihydrochloride by treatment with a 10% ethanolic solution of hydrogen chloride. This gives 4-aminomethyl-1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine dihydrochloride, which is waxy and melts at 80°.

Example 14: Ethyl 1-(2'-hydroxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate
8.3 g (0.015 mol) of ethyl 1-(2'-thexyldimethylsilyloxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate (Example 13b) are dissolved in 120 ml of 1% conc. hydrochloric acid in ethanol, and the solution is heated under reflux for 12 hours. After cooling it is evaporated, the residue is taken up in methylene chloride, and the extract is washed with saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated again. The resulting oil is chromatographed over silica gel 60 (8:2 ethyl acetate/petroleum ether). The pure fractions afford the title compound as an oil; mass spectrum: 383 and 184.

Example 15: 1-(2'-Hydroxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylic acid
2 g (0.005 mol) of ethyl 1-(2'-hydroxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate (Example 14) are dissolved in 30 ml of ethanol, 5 ml (0.01 mol) of 2 N sodium hydroxide solution are added and the mixture is heated under reflux for 4 hours. It is worked up by cooling to 0°, neutralizing with 5 ml (0.01 mol) of 2 N hydrochloric acid and distilling off the alcohol in a rotary evaporator. The aqueous residue is extracted with methylene chloride and the organic phase is washed with water, dried over sodium sulfate and evaporated. The solid residue is recrystallized from methanol. The title compound melts at 198-200°, mass spectrum: 355 and 156.

Example 16: 4-Hydroxymethyl-1-(2'-hydroxy-1'-tetradecyl)-4- methylpiperidine hydrochloride
0.15 g (0.004 mol) of lithium aluminium hydride are initially placed in 15 ml of abs. ether under nitrogen. A solution of 0.8 g (0.002 mol) of ethyl 1-(2'-hydroxy-1'-tetradecyl)-4-methylpiperidine-4-carboxylate (Example 14) is added dropwise and stirring is continued for 12 hours. 0.15 ml of water, 0.15 ml of 15% sodium hydroxide solution and 0.45 ml of water are added successively to the reaction mixture, and the mixture is diluted somewhat with ether and filtered. The filtrate is dried over sodium sulfate and evaporated. The

residue is converted into the hydrochloride by means of 10% ethanolic hydrogen chloride; melting point 100° (waxy compound).

Example 17: 4-Hydroxymethyl-1-(2'-hydroxy-1'-tetradecyl)-piperidine hydrochloride

0.76 g (0.02 mol) of lithium aluminium hydride are initially placed in 50 ml of abs. ether under nitrogen. A solution of 3.69 g (0.01 mol) of ethyl 1-(2'-hydroxy-1'-tetradecyl)-piperidine-4-carboxylate (60 ml of ether) (Example 11) is added dropwise and stirring is continued for 1.5 hours. 0.75 ml of water, 0.75 ml of 15% sodium hydroxide solution and 2.28 ml of water are added successively to the reaction mixture, and the mixture is diluted somewhat with ether and filtered. The filtrate is dried over sodium sulfate and evaporated. The residue is recrystallized from petroleum ether (melting point of the free base 40-42°). The hydrochloride is obtained by dissolving the free base in a little ethanol, adding 10% ethanolic hydrogen chloride solution and concentrating; melting point 110°.

Example 18: 4-Cyano-1-(2'-decanoyloxy-1'-tetradecyl)-4-phenylpip eridine hydrochloride

15.92 g (0.04 mol) of 4-cyano-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine (Example 1e) are initially placed in 40 ml of methylene chloride, and 11.4 g (0.06 mol) of decanoyl chloride are added dropwise at room temperature. The reaction mixture is stirred for 15 minutes at room temperature and then heated under reflux for 30 minutes. After cooling, the mixture is washed with saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated. The residue is purified by chromatography over silica gel 60 (3:7 ethyl acetate/petroleum ether). The hydrochloride is obtained by treating the pure fractions with ethanolic hydrogen chloride; melting point 63-65°.

Example 19: 4-Aminomethyl-1-(2'-decanoyloxy-1'-tetradecyl)-4- phenylpiperidine dihydrochloride

33.6 g (0.06 mol) of 4-cyano-1-(2'-decanoyloxy-1'-tetradecyl)-4-phenylpiperidine (Example 18) are hydrogenated under normal pressure in 500 ml of acetic acid by means of 3.6 g of platinum oxide. The reaction ceases after 14 hours, the catalyst is filtered off and the filtrate is evaporated. The residue is taken up in methylene chloride and the solution is washed with saturated sodium bicarbonate solution, dried over sodium sulfate and evaporated again. Chromatography over silica gel 60 using 7:3 methylene chloride/methanol affords the free base of the title compound (oil), which is dissolved in ethanol and converted into the hydrochloride by adding 10% ethanolic hydrogen chloride; melting point 85-87°.

Example 20: 4-Hydroxymethyl-1-(3'-hydroxy-1'-tetradecyl)-piperidine

A solution of 1.2 g (3.1 mmol) of ethyl 1-(3'-hydroxymyristoyl)-piperidine-4-carboxylate in 20 ml of abs. THF is added dropwise, at 50° and with the exclusion of moisture, to a stirred suspension of 0.25 g (6.6 mmol) of lithium aluminium hydride in 10 ml of abs. THF. The mixture is stirred for 16 hours at this temperature. After it has cooled, 10 ml of 5 N sodium hydroxide solution and 20 ml of water are added cautiously and the mixture is extracted with twice 50 ml of ether. The ether solutions are washed with water, dried over sodium sulfate and evaporated. This gives the title compound as a yellowish oil, Rf value = 0.4 (silica gel thin layer plates, 40:20:1 methylene chloride : methanol : conc. ammonia).

The starting compound is prepared as follows:

1.57 g (10 mmol) of ethyl piperidine-4-carboxylate and 5.0 g (20 mmol) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) are added to a solution of 2.4 g (10 mmol) of 3-hydroxymyristic acid in 100 ml of dimethylformamide, and the mixture is stirred for 30 hours at 50°. The reaction mixture is evaporated and the residue is chromatographed over silica gel using 1:1 methylene chloride/ethyl acetate. This gives ethyl 1-(3'-hydroxymyristoyl)-piperidine-4-carboxylate as a yellowish oil, Rf value = 0.32 (silica gel thin layer plates, 1:1 methylene chloride : ethyl acetate).

Example 21: 4-Aminomethyl-1-(3'-hydroxy-1'-tetradecyl)-4-phenylpiperidine oxalate

A solution of 0.613 g (4.6 mmol) of aluminium trichloride in 5 ml of THF is added, with the exclusion of moisture, to a stirred suspension of 0.175 g (4.6 mmol) of lithium aluminium hydride in 5 ml of THF, and the mixture is heated to 50°. A solution of 0.76 g (1.84 mmol) of 4-cyano-1-(3'-hydroxymyristoyl)-4-phenylpiperidine in 10 ml of THF is added dropwise to this mixture and stirring is continued for 16 hours. The reaction mixture is worked up analogously to Example 20 and the resulting product is crystallized as the oxalate from methanol; melting point 190-192°.

The starting compound is prepared as follows:

1.38 ml (10 mmol) of triethylamine, 2.3 g (10 mmol) of 4-cyano-4-phenylpiperidine hydrochloride and 5.0 g (20 mmol) of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) are added successively to a solution of 2.4 g (10 mmol) of 3-hydroxymyristic acid in 100 ml of dimethylformamide, and the mixture is stirred for 30 hours at 50°. The reaction mixture is evaporated and the residue is chromatographed over 250 g of silica gel

using 1:1 methylene chloride/ethyl acetate. This gives 4-cyano-1-(3'-hydroxymyristoyl)-4-phenylpiperidine as a yellow oil.

Example 22: 4-(N-Acetylaminomethyl)-1-(2'-hydroxy-1'-dodecyl)-4-phenylpiperidine hydrochloride

2 g (0.0053 mol) of 4-aminomethyl-1-(2'-hydroxy-1'-dodecyl)-4-phenylpiperidine (Example 2d), 10 ml of pyridine and 10 ml of acetic anhydride are stirred for 16 hours at room temperature. After cooling, the mixture is diluted with 150 ml of ice water and allowed to stand for 45 minutes. After extraction with ethyl acetate the organic phase is washed with 2 N hydrochloric acid, 2 N sodium hydroxide solution and saturated sodium chloride solution, dried over sodium sulfate and evaporated. The residue is chromatographed over silica gel 60 (gradient: 80:20 to 40:60 toluene/ethyl acetate). The fractions containing the diacetyl compound are evaporated, the residue is dissolved in 32 ml of methanol, and 1.21 g (0.00875 mol) of potassium carbonate in 8 ml of water are added. 100 ml of a saturated sodium chloride solution are added to the yellow solution after it has been stirred for 17 hours at room temperature, and the mixture is extracted with ethyl acetate. The organic phase is washed with saturated sodium chloride solution, dried over sodium sulfate and evaporated. Chromatographing the residue over silica gel 60 (gradient: pure chloroform to 95:5 chloroform/methanol) and recrystallizing the pure fractions from methylene chloride/ether/petroleum ether affords the title compound as the free base (melting point 68-70°). The hydrochloride is obtained by the addition of ethanolic hydrogen chloride and crystallization from ether; melting point 70-75°.

Example 23: Capsules containing 0.25 g of active ingredient, for example one of the compounds of Examples 1-22, can be prepared as follows:

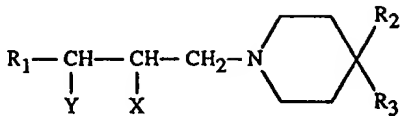
Composition (for 5000 capsules)

Active ingredient	1250 g
Talc	180 g
Wheat starch	120 g
Magnesium stearate	80 g
Lactose	20 g

The pulverulent substances are forced through a sieve having a mesh width of 0.6 mm and are mixed. 0.33 g portions of the mixture are filled into gelatin capsules by means of a capsule filling machine.

WHAT IS CLAIMED IS:

1. A compound of the formula I



(I)

in which R_1 is C_1-C_{30}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano or lower alkyl which is substituted by hydroxyl, lower alkoxy, acyloxy, amino, lower alkylamino, di-lower alkylamino or acylamino; R_3 is hydrogen, lower alkyl or aryl; one of the radicals X and Y is hydroxyl, lower alkoxy or acyloxy and the other of the radicals X and Y is hydrogen; or both radicals X and Y can also be hydrogen, if R_2 is cyano or lower alkyl substituted by amino or acylamino and R_1 is C_2-C_{30}alkyl; and salts thereof.

2. A compound of the formula I according to claim 1, in which R_1 is C_1-C_{19}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, N-lower alkylcarbamoyl, N,N-di-lower alkylcarbamoyl, cyano or lower alkyl which is substituted by hydroxyl, lower alkoxy, lower alkanoyloxy, amino, lower alkylamino, di-lower alkylamino or lower alkanoylamino; R_3 is hydrogen, lower alkyl or phenyl; one of the radicals X and Y is hydroxyl, lower alkoxy, C_1-C_{18}alkanoyloxy, carbamoyloxy, N-lower alkylcarbamoyloxy, N-phenyl-lower alkylcarbamoyloxy or N-phenylcarbamoyloxy and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is cyano or lower alkyl substituted by amino or lower alkanoylamino and R_1 is C_2-C_{19}alkyl, phenyl radicals being unsubstituted or substituted by lower alkyl, halogeno-lower alkyl, hydroxyl, lower alkoxy, lower alkanoyloxy, halogen and/or nitro; and salts thereof.

3. A compound of the formula I according to claim 1, in which R_1 is C_1-C_{15}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, cyano or lower alkyl which is substituted by hydroxyl, amino or lower alkanoylamino; R_3 is hydrogen, lower alkyl or phenyl; one of the radicals X and Y is hydroxyl, C_1-C_{12}alkanoyloxy or N-phenyl-lower alkylcarbamoyl-oxy and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is aminomethyl and R_1 is C_2-C_{15}alkyl; and salts thereof.

4. A compound of the formula I according to claim 1, in which R_1 is C_7-C_{15}alkyl; R_2 is carboxyl, lower alkoxycarbonyl, carbamoyl, hydroxymethyl, aminomethyl or lower alkanoylaminomethyl; R_3 is hydrogen, methyl or phenyl; one of the radicals X and Y is hydroxyl and the other of the radicals X and Y is hydrogen, or both radicals X and Y can also be hydrogen, if R_2 is aminomethyl; and salts thereof.

5. A compound of the formula I according to claim 1, in which R_1 is C_7-C_{15}alkyl, R_2 is aminomethyl, R_3 is phenyl and (a) X is hydroxyl and Y is hydrogen, or (b) X is hydrogen and Y is hydroxyl, or (c) X and Y are hydrogen; and salts thereof.

6. 4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-piperidine and pharmaceutically acceptable salts thereof according to claim 1.

7. 4-Aminomethyl-4-phenyl-1-tetradecylpiperidine and pharmaceutically acceptable salts thereof according to claim 1.

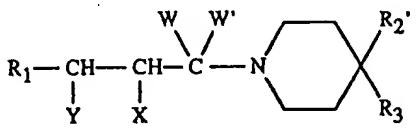
8. 4-Aminomethyl-1-(2'-hydroxy-1'-tetradecyl)-4-phenylpiperidine and pharmaceutically acceptable salts thereof according to claim 1.

9. 4-Aminomethyl-1-tetradecylpiperidine and pharmaceutically acceptable salts thereof according to claim 1.

10. A pharmaceutical formulation containing a compound according to any one of claims 1 to 9 and at least one pharmaceutically acceptable carrier.

11. A process for the preparation of a compound of the formula I according to claim 1, which comprises

(a) reducing a compound of the formula II

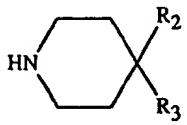


(II)

in which R_1, R_3, X and Y are as defined under formula I, R_2' is a group which can be converted by reduction into a radical R_2, or, if W and W' together are oxo, R_2' is also a

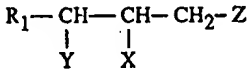
radical R_2 as defined under formula I, and W and W' together are an oxo group or are two hydrogen atoms, or

(b) alkylating a compound of the formula III



(III)

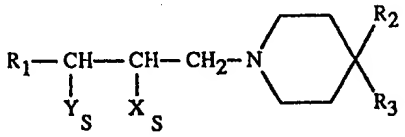
in which R_2 and R_3 are as defined under formula I, by means of a compound of the formula IV



(IV)

in which R_1, X and Y are as defined under formula I and Z is a nucleofugic detachable group and X and Z together can also be an epoxy group, or

(c) in order to prepare compounds of the formula I in which X or Y is hydroxyl, removing the hydroxyl protective group in a compound of the formula V



(V)

in which R_1, R_2 and R_3 are as defined under formula I, one of the radicals X_s and Y_s is a hydroxyl group protected by a protective group and the other of the radicals X_s and Y_s is hydrogen; and/or, if desired, converting a resulting compound of the formula I into another compound of the formula I, and/or, if desired, converting a resulting salt into the free compound or into another salt, and/or, if desired, converting a resulting free compound of the formula I into a salt, and/or resolving a resulting mixture of isomeric compounds of the formula I into the individual isomers.

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